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| (54) Title: COMBINED ANALGESIC DELIVERY METHODS FOR PAIN MANAGEMENT   |  |   |  |
| (57) Abstract<br><br>Methods of providing pain relief are described. The methods comprise the administration of an analgesic compound at a level sufficient to provide relief of continuous base-line pain. A second administration of analgesic to provide a periodic and temporary increase in level of analgesic sufficient to treat incident pain is also described. Methods of delivery of the analgesic compounds include the use of transdermal, iontophoretic, and nasal drug delivery vehicles.  |  |   |  |

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COMBINED ANALGESIC DELIVERY METHODS  
FOR PAIN MANAGEMENT

BACKGROUND OF THE INVENTION

Pain is the most common symptom of disease. Although the nature, location and etiology of pain differ in each case, approximately half of all patients who visit a physician have a primary complaint of pain. Nearly all post-operative patients experience some degree of pain.

Generally, pain is treated by the administration of analgesic drugs. Analgesic drugs can be divided into three groups: non-narcotic analgesics, narcotic analgesics, and adjuvant analgesics. The first group, non-narcotic analgesics, includes drugs such as aspirin, acetaminophen, and nonsteroidal anti-inflammatory drugs (NSAIDs) such as ketorolac, piroxicam, ibuprofen, minoxipirofen and diclofenac. Non-narcotic analgesics are generally used for the management of mild to moderate pain. The long-term use and dosage range of non-narcotic analgesics is limited by gastrointestinal and hematologic side effects.

If the use of non-narcotics fails to effectively control pain, or if the drugs are poorly tolerated, then generally a

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narcotic analgesic is selected for pain management. Narcotic analgesics activate opiate receptors in the central and peripheral nervous systems and include drugs such as methadone, fentanyl and buprenorphine. The effective use of  
5 narcotic analgesics requires a balancing of the desirable effect of pain relief with the undesirable side effects of nausea, vomiting, mental clouding, sedation, tolerance, and physical dependence. These undesirable effects impose a practical limit on the dose one can give a particular patient.

- 10 When a narcotic analgesic is used in conjunction with a non-narcotic analgesic, effective pain relief may be achieved while maintaining a low enough dose of the narcotic analgesic to minimize side effects. A further advantage in combining the use of narcotic and non-narcotic analgesics is that, in  
15 patients with severe pain, non-narcotic analgesics potentiate the effects of narcotic analgesics. For example, aspirin or acetaminophen potentiate the analgesic effect of codeine.

The adjuvant analgesics include several different categories of drugs including anticonvulsants, antihistamines, amphetamines, tricyclic antidepressants, and steroids. As  
20 is true with certain non-narcotic analgesics, adjuvant analgesics when used in conjunction with narcotic analgesics result in improved analgesic effects than when either drug is used alone. For example, the tricyclic antidepressants  
25 both enhance the analgesic effects of morphine and have independent analgesic properties. The analgesic effects of the tricyclic antidepressants occur independently of their antidepressant properties.

- 30 Frequently, analgesics are delivered by injection to provide a rapid onset of therapeutic effect and accompanying immediate relief of symptoms. It is also common practice to obtain prolonged analgesia by producing sustained blood concentrations by constant intravenous or subcutaneous infusions with additional analgesia made available by

administration of intravenous bolus doses of analgesic. These methods of drug delivery generally occur in the hospital setting.

One disadvantage with bolus injection methods, in addition  
5 to the initial pain caused by the injection itself, is that drug action (efficacy) is limited in time due to the fact that drug input is not continuous and that the blood levels will decline in accordance with the pharmacokinetics of the analgesic. Another disadvantage is that a bolus dose may  
10 result in the potential risk of elevating the concentration of drug in the plasma into the toxic range. Still another disadvantage with these methods of analgesia delivery is that they require that administration of the drug be performed by trained medical personnel. Other inadequacies exist with  
15 conventional injection treatments. For example, one study showed that, despite treatment with narcotic analgesics, 75% of hospitalized patients experienced moderate or severe pain, thus indicating undertreatment (Marks RM, Sachar EJ. Ann Intern Med 78:173-82 (1973)). For infusion techniques the  
20 primary disadvantage is the need for constant intravenous access.

In recent years, some of the disadvantages attendant with standard intravenous drug delivery have been alleviated through the use of sophisticated electronic pumps that can  
25 be activated by the patient for on-demand drug delivery. These electronic devices have evolved from nonambulatory to ambulatory implantable systems. Numerous studies have been done to assess the safety and efficacy of patient-controlled analgesia (PCA). These studies generally show that PCA  
30 results in improved pain relief, less sedation, lower levels of narcotic consumption, and greater patient satisfaction. However, implantable systems can have disadvantages. Implantation procedures are invasive and expensive and the devices can be bulky. The proper usage of these devices may  
35 be difficult for some patients to learn. Since pumps have needles, there is a possibility of infection at the injection

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site, requiring the site to be changed; and like all infusion techniques, a constant intravenous access is required.

Another method by which a patient can control pain management is through the oral delivery of analgesics. While this method of delivery eliminates some of the problems attendant with intravenous injections, such as discomfort and the need for trained medical personnel, it is generally insufficient in providing immediate pain relief since pills are sometimes slow to act. In addition, many oral analgesics often have bioavailability problems and may cause gastrointestinal irritation. Therefore, in many instances, other modes of delivery (e.g. transdermal, parenteral therapy, nasal) are essential.

Given the deficiencies attendant with the prior art of pain management, there is a continued need to increase the alternatives available for the delivery of analgesics. One mode of administering analgesics that is receiving increased attention is the use of transdermal patches. For example, the transdermal delivery of the analgesic fentanyl in the treatment of postoperative pain is disclosed by Gourlay et al in Pain, 37:193-202 (1989). The transdermal delivery of ketorolac is disclosed in Pharmaceutical Research, 5:457-462 (1988). Transdermal patches have the ability of delivering controlled amounts of drugs to patients for extended periods of time. Oftentimes a patch is formulated with the drug to be delivered and an enhancer which increases the permeability of the drug through the patients' skin.

Despite present efforts, the use of transdermal delivery of analgesics for the treatment of pain is of limited use for several reasons. First, it is often difficult, even with the use of enhancers, to get high enough levels of analgesics in the blood due to the limited permeability of the skin. This inadequacy is exacerbated in the situation where transdermal route of administration is the mode by which an analgesic drug is first delivered. For example, Gourlay et al, supra, have

shown that during the first 12 hours of transdermal delivery of fentanyl, supplementary injections of pethidine are required by all patients for the relief of pain. A second disadvantage of simple transdermal drug delivery is that when  
5 very large amounts of drug are delivered, skin irritation often results. A third disadvantage arises because the use of simple transdermal delivery is not readily amenable to individualized treatment since there is normally a limited range of doses available. Further, pain management often  
10 requires individually titrated dosage regimes because efficacy is not always predictable on a mg dose/kg basis. Another distinct disadvantage with transdermal delivery of analgesics is that while a fairly constant blood level of drug is maintained, it is often insufficient to provide rapid relief  
15 from occasional episodes of more severe pain.

Another method for the administration of analgesics that has received limited attention is nasal delivery. Currently, there are no commercial products that provide for the nasal delivery of analgesics; however, the nasal delivery of  
20 morphine and meperidine is disclosed in US Patent Nos. 4,464,378 and 4,973,596, respectively. Generally, drug formulations for nasal delivery are solutions (for use as drops or as a spray), suspensions, ointments, or gels. Nasal administration can be carried out using a single dose nasal  
25 administrator. Its main advantage is that it can provide rapid absorption and thus immediate relief of pain. As with transdermal delivery, the administration of analgesics by nasal delivery presents several limitations. Only a limited amount of drug can be given before irritation occurs.  
30 Irritation also poses a problem if the drug is administered repeatedly and frequently, for example, at intervals of less than every 1 hour or more than 5 to 10 times in any one day.

Another alternative in delivering analgesics for pain management is the use of iontophoresis techniques.  
35 Iontophoresis employs electromotive forces to move ionized or unionized drug molecules through the skin. [Iontophoresis



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works to a lesser extent for unionized molecules by a process called electroosmosis]. Iontophoresis is achieved by the application of a voltage potential against the surface of a patient's skin in conjunction with a drug reservoir compartment. Upon initiation of the potential, an ionic current will flow to and through the skin. Associated with this current flow will be the movement of the ionized drug molecules.

Iontophoresis devices, like transdermal patches, have the ability to deliver controlled amounts of drug to patients for extended periods of time. However, iontophoresis has the additional advantage that it may provide a more rapid onset of action in accordance with that attained by nasal administration. Further, since delivery is generally proportional to the applied current, the steady state blood levels of drug can be varied according to patient needs and may, in fact, represent a non-invasive alternative to PCA techniques. As with nasal and transdermal delivery, a limitation in the use of iontophoresis for the delivery of analgesics is the potential for irritation at the delivery site. There is also the possibility of inducing sensitization (allergic contact dermatitis) via repeated usages.

Accordingly, it is an immediate objective of this invention to provide both a novel and useful method for treating pain conditions, which method overcomes the disadvantages of the prior art.

It is another object of the invention to provide a method for the administration of analgesics that does not require the continuous involvement of medical personnel for drug administration.

Another object of this invention is to provide a method of administration of analgesics that is effective in providing relief from bouts of elevated pain levels which may be experienced by a patient, yet limits the possibility of

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toxicity problems often present with injection methods due to large priming doses.

It is a further object of this invention to provide a method of administration of analgesics that is less invasive than injection and intravenous methods yet minimizes the irritation associated with transdermal delivery and frequent nasal and iontophoretic delivery.

It is also an object of this invention to provide a noninvasive approach to medically establish or define the individual level of pain experienced by patients in order to provide better therapy, given that pain cannot be approached on a mg/kg basis.

These and other objects and features of the invention will be apparent to those skilled in the art from the following detailed description and appended claims.

None of the foregoing references is believed to disclose the present invention as claimed and is not presumed to be prior art. The references are offered for the purpose of background information.

20

#### SUMMARY OF THE INVENTION

The above objects of the invention are realized through a method of providing pain relief. This method comprises administering an analgesic to a person in need of pain relief by a first drug delivery means to provide a base-line level of analgesia, and periodically administering the same or different analgesic by a second drug delivery means to provide rapid onset of analgesia for the relief of periodic bouts of more intense pain not sufficiently treated by the first drug delivery means.

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In one embodiment of the present invention, the first drug delivery means is a transdermal patch which provides baseline analgesia to a person in need of pain relief for a period of about 12 hours or more, and the second drug delivery means  
5 is a nasal formulation which rapidly and temporarily increases blood analgesic levels to provide relief from periodic bouts of more intense pain not sufficiently treated by the transdermal patch. Alternatively the second drug delivery means is a high-current iontophoresis device.

10 In another embodiment of the present invention, the first drug delivery means is a low-current iontophoresis device which provides baseline analgesia to a person in need of pain relief for a period of about 12 hours or more, and the second drug delivery means a nasal formulation which rapidly and  
15 temporarily increases blood analgesic levels to provide relief from periodic bouts of more intense pain not sufficiently treated by the iontophoresis. Alternatively, the second drug delivery means is a high-current iontophoresis device.

20 BRIEF DESCRIPTION OF THE DRAWINGS

FIG. 1 is a plot showing the two different types of pain which are generally perceived over a period of time by a patient in need of pain management.

FIG. 2a plots plasma concentration of analgesics versus time  
25 after intravenous, oral, and nasal administration.

FIG. 2b plots plasma concentration of analgesics versus time after iontophoresis, and transdermal delivery.

FIG. 3 shows a transdermal patch having an impermeable backing and an adhesive polymer matrix layer in which an analgesic  
30 is dispersed.

FIG. 4 shows a transdermal patch having an impermeable backing, an analgesic depot, and a drug-permeable membrane.

FIG. 5 shows a transdermal patch having an impermeable backing, a polymer matrix in which an analgesic is dispersed, and a drug-permeable membrane.

#### DESCRIPTION OF THE PREFERRED EMBODIMENTS

5 In accordance with the practice of the invention, there is provided a method of providing pain relief which comprises administering an analgesic by a drug delivery means to provide a base-line level of analgesia for a period of about 12 hours or more, and administering the same or different analgesic  
10 by a second drug delivery means to provide rapid onset of temporarily increased levels of analgesia. Together, the combined delivery methods provide a therapeutically effective level of analgesia throughout a regimen of pain management.

The delivery of analgesics by a first mode of delivery in  
15 combination with a second mode of delivery, as described in the following discussion, results in a synergistic effect and better control of pain on an individual basis. As a result, the relief and control of pain obtained exceeds that which would be expected by simple addition of the effect of each  
20 delivery mode. Accordingly, two sub-optimal drug formulations when used together can be effective in producing analgesia.

In using analgesics for the management of pain relief, it is helpful to be aware of the type of pain the patient is experiencing or will likely experience. Pain can be depicted  
25 conceptually as in Figure 1. There is often a "base-line" level of perceived pain that remains fairly constant over a period of time, for example 8-24 hours post-operation. In addition to this base-line level of pain, a patient may experience periodic bouts of more intense pain. This form  
30 of pain is referred to herein as "incident pain." Ideally, the minimum amount of analgesic necessary to achieve effective relief from pain should be delivered. However, variations in the level of pain experienced by a patient generally result in the patient being overdosed throughout much of the

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treatment, while being undertreated for bouts of incident pain.

From Figures 2a and 2b it can be seen that different modes of analgesic delivery result in varying analgesia blood level profiles. If Figures 1, 2a, and 2b are superimposed, it is perceived that certain modes of analgesia delivery are particularly suited for providing base-line levels of analgesics, while others appear particularly amenable for treatment of incident pain. The term "base-line level of analgesic" as used herein refers to the blood level of drug necessary to provide relief from base-line pain. A base-line level of analgesic is achieved by a drug delivery means that is capable of sustaining a relatively constant level of analgesic in a person's system for an extended period of time. Thus, as is apparent from Figure 2b, a rate-controlled drug delivery device such as a transdermal patch or a low-current iontophoretic device is capable of providing a base-line level of analgesic. Because perceived pain varies greatly between individuals, the dose of analgesic administered to treat base-line pain will be determined by the attending physician based on his knowledge of the patient, the type of pain involved, and the analgesic to be administered.

Because of the controlled rate of release of analgesic from a transdermal patch, this mode of delivery is often appropriate for treatment of base-line pain. However, in order to treat incident pain, higher blood levels are required for a short period of time. In addition to increasing the potential for side effects, the large dose necessitates the use of either very large patches or irritating skin permeability enhancers or both in order to get enough drug in the patient's blood, which may prove to be unacceptable for many patients. Another limitation is that transdermal delivery per se is not amenable to delivering or increasing blood levels rapidly upon demand in such situations.

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The drawbacks of transdermal delivery of analgesics can be reduced or eliminated when another method of analgesic delivery is used to treat periodic bouts of incident pain, while transdermal delivery of the same analgesic or a different analgesic is used concurrently to provide relief from the underlying base-line pain. Looking at Figures 1, 2a, and 2b, it becomes apparent that certain drug delivery modes are aptly suited for treatment of incident pain because they can rapidly increase levels of analgesic above base-line level. Again, because perceived pain levels vary greatly between individuals, the amount of drug delivered in one dosage for the treatment of incident pain will be determined by the attending physician based on his knowledge of the patient, the type of pain involved, and the analgesic to be delivered.

By combining different drug delivery means to individually treat baseline and incident pain, the total amount of analgesics used to treat pain as compared to conventional treatments can be reduced. For example, the dose of drug delivered transdermally to treat base-line pain can be reduced up to a factor of 2, and thus results in the use of smaller patches. By lowering the levels of drug administered transdermally the resulting side-effects often associated with transdermal delivery of analgesics, such as irritation and rashes, are reduced.

The method of delivery that is used to treat incident pain in conjunction with the use of a rate-controlled drug delivery device to treat baseline pain is one that rapidly increases the level of analgesics above base-line level, yet does not result in prolonged elevated blood levels of drug. The term "prolonged elevated blood levels of drug" as used herein refers to the situation where the constant steady state blood concentration would be increased. The duration of time in which blood levels of analgesic are elevated will generally depend upon the half-life of the drug. Thus, for the treatment of incident pain, it is preferable to deliver a drug

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that has a half-life of less than about 6 hours so that total blood level of analgesic is only temporarily above base-line level. Generally, the analgesia delivery method used to treat incident pain will be under the control of the patient, and  
5 as many doses as needed for relief from incident pain will be taken by the patient within a physician's guidelines.

Preferable analgesic delivery modes for the treatment of incident pain are those that are easy for the patient to learn  
10 and rapidly increase analgesic levels above base-line levels. Nasal and high-current iontophoretic methods fall within this category. With nasal delivery, the rich supply of blood vessels in the nasal mucosa greatly enhances drug absorption and provides rapid onset of analgesia, usually within 15 to  
15 30 minutes. As with nasal delivery, rapid onset of analgesia can be achieved by iontophoresis within about the same amount of time. The duration of time in which blood levels of analgesic delivered by iontophoresis are elevated will depend upon, in addition to the half-life of the drug, the length  
20 of time the iontophoresis system is worn by the patient.

By using the methods of the present invention and combining the use of a transdermal patch or low-current iontophoretic system to treat base-line pain and an alternative method of delivering an analgesic to treat incident pain such as by  
25 nasal delivery or high-current iontophoresis, the amount of drug delivered will generally be less than the amount of drug that would be normally required for pain management when only one method of delivery is used to treat both incident and base-line pain. Thus the potential for irritation that often  
30 results when nasal delivery or iontophoresis of analgesics is used as the sole method of pain relief is substantially decreased.

Another benefit of the methods of the present invention is the reduction in tolerance and dependence of analgesics  
35 because the pain receptors are not continuously exposed to constant high levels of one drug. The problem of tolerance

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is frequently seen in pain management therapy. If a drug is administered to a patient relatively continuously, the neuro-receptors responsible for the analgesic effect become tolerant to the drug. Thus, increasing levels of drug are required to achieve the same therapeutic effect. With time, the blood level of drug may become so high that it becomes toxic and drug therapy must be discontinued. The receptors then gradually adjust to the absence of drug and then after a period of time the drug can again be used. However, tolerance is a cyclic process, and the drug will need to be discontinued again once drug levels become toxic.

The problem of tolerance is greatly reduced if the amount of drug delivered is low and in particular, if blood levels of drug are allowed to fluctuate so that high blood levels are followed by low blood levels. The problem of patient dependence on analgesic drugs is particularly a problem with the narcotic analgesics. This can also be reduced by delivering the drugs in a non-constant fashion.

Still another advantage of combining methods of analgesic delivery in a pain management regimen in order to provide individualized treatment of incident pain and base-line pain is realized when synergism occurs among two different analgesics delivered. Synergism allows even a further reduction in drug dose required for the effective relief of pain.

This methods of the present invention encompass the use of transdermal formulations or low-current iontophoresis devices in combination with nasal or high-current iontophoretic analgesic formulations. To illustrate the invention, the preparation of the transdermal, nasal, and iontophoretic formulations are first described separately followed by a description of the combined use of these formulations pursuant to the methods of the present invention.

#### Transdermal Drug Delivery



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Transdermal drug delivery involves the permeation of the drug through a patient's skin. The stratum corneum, a thin layer of dense, highly keratinized cells, is the primary obstacle in drug permeation. A few drugs, such as fentanyl, are able to penetrate the skin at a useful rate by themselves. But frequently, to increase permeability of the stratum corneum, permeation enhancers are employed. Various compounds for enhancing the permeability of skin are known in the art. U.S. Pat. Nos. 4,006,218, 3,551,554 and 3,472,931, for example, respectively describe the use of dimethylsulfoxide (DMSO), dimethyl formamide (DMF) and N,N-dimethylacetamide (DMA) to enhance the absorption of pharmacologically active agents through the stratum corneum. Other compounds which have been used to enhance skin permeability include decylmethylsulfoxide, diethylene glycol monoethyl ether, polyethylene glycol monolaurate (U.S. Pat. No. 4,568,343), glycerol monolaurate (U.S. Pat. No. 4,746,515) ethanol (U.S. Pat. No. 4,379,454), eucalyptol (U.S. Pat. No. 4,440,777), and lecithin (U.S. Pat. No. 4,783,450).

An analgesic can be delivered transdermally in a variety of compositions. The composition may be applied directly to the skin in any of the forms known in the pharmaceutical arts, such as creams, lotions, gels or pastes. However, a preferable method of transdermal delivery is with a skin patch. The design of transdermal patches is discussed in various reviews and books such as Baker, R.W., Controlled Release of Biologically Active Agents, John Wiley and Sons, New York, (1987). Referring to FIG. 3., one type of transdermal patch is referred to as an adhesive matrix type patch 1, and comprises an impermeable backing layer, 2, and a matrix layer 3, that contains the analgesic and an enhancer. The matrix layer may be a microporous material impregnated with solvent enhancer and dissolved analgesic. A variety of polymers that might be used as a microporous matrix are known in the art. Typically, a microporous polypropylene, such as Celgard, obtainable from Celanese Corp., Charlotte, N.C., might be used.

Another type of patch which can be used for the effective delivery of analgesics is the reservoir-type. Such systems are already known in the art and are taught, for instance in U.S. Patent Nos. 4,379,454, and 4,943,435, incorporated herein  
5 by reference. Briefly, referring to FIG. 4, the reservoir type transdermal patch, 4, comprises an impermeable backing layer, 2, an analgesic reservoir, 5, a drug-permeable membrane, 6, and an adhesive layer.

A third type of patch is a monolithic system, in which a non-  
10 porous matrix, is swollen with dissolved enhancer and analgesic. The choice of monolithic carrier depends on the enhancer material. Materials which might be used are, for example, acrylate and methacrylate copolymers. Monomers of these materials such as hydroxy ethyl methacrylate dissolved in a  
15 mixture of drug and enhancer can be polymerized by a suitable free radical polymerization reaction to yield a cross-linked gel containing drug and enhancer. By varying the concentration of the cross-linking agent or the chemistry and concentration of the monomer the density of the gel is  
20 increased. Dense gels prepared from high concentrations of monomers and high concentrations of cross-linked agents release the enhancer more slowly than less dense gels. The chemistry of these reactions and the monomers and cross-linked agents that can be used are discussed on pages 179-184 in  
25 Baker, R.W., Controlled Release of Biologically Active Agents, John Wiley and Sons, New York, (1987).

One embodiment of the monolithic matrix type transdermal patch is shown in FIG. 5. The transdermal patch, 7, comprises an impermeable backing layer, 2, a monolithic matrix layer, 3,  
30 an optional drug permeable membrane layer, 6, and an adhesive layer 7.

The patch embodiments described above may be held in contact with the skin in a variety of ways, such as by means of a porous or non-porous overlay coated wholly or partly with  
35 adhesive, by an adhesive layer between the patch and the skin,

or by an annulus of adhesive around the periphery of the patch. Representative adhesives used for transdermal patches include: acrylic-based pressure-sensitive adhesives manufactured by many companies including 3M and Avery; 5 polyisobutylene with blends of low and high molecular weight polymers (Exxon, Vistanex); and silicone-based adhesives manufactured by Dow Corning (355 and BioPSA). Other variations in the basic geometries described, to assist for example, in retaining good skin contact or an occlusive 10 environment are also intended to be within the scope of the invention.

In choosing an analgesic that is suitable for transdermal delivery it is necessary to consider both biological and physico-chemical aspects of the drug. The analgesic needs 15 to have adequate skin permeability. Factors attributing to improved permeability include low molecular weight, low melting point, and moderate oil and water solubility. Table I lists these factors of various analgesics.

TABLE I

| Compound               | oral dose for<br>analgesia<br>(mg/day) | mean<br>half-life<br>(hours) | water<br>solubility<br>mg/ml | MW    | MP<br>°C | pKa |
|------------------------|--|------------------------------|------------------------------|-------|----------|-----|
| acetylsalicylic acid   | up to 4000                             | 0.25                         | 3.3                          | 180.2 | 135      | 3.5 |
| acetaminophen          | up to 4000                             | 2                            | slightly                     | 151   | 169      | 9.5 |
| Ibuprofen              | 2400-3200                              | 2                            | insoluble                    | 206.3 | 76       | 4.4 |
| Naproxen Sodium        | 500-1000                               | 13                           | soluble                      | 252   | 245      | 4.2 |
| Meperidine HCl         | 300-900                                | 3.2                          | soluble                      | 284   | 187      | 8.7 |
| Pentazocaine HCl       | 600                                    | 3.6                          | 23.8                         | 285   | 146      | 8.5 |
| Papaverine HCl         | 600                                    |                              | 25                           | 376   | 222      | 6.4 |
| Codeine Sulfate        | 240                                    | 3.5                          | 33                           | 697   |          | 8.2 |
| Indomethacin           | 150-200                                | 4.5                          | insoluble                    | 358   | 155      | 4.5 |
| Morphine HCl           | 120-240                                | 2-3                          | 57                           | 322   | 200      | 8.0 |
| Ketorolac Tromethamine | 120-150                                | 4-6                          | 720                          | 377   | 161      | 3.5 |
| Methadone HCl          | 40                                     | 23-47                        | 120                          | 346   | 235      | 8.3 |
| Piroxicam              | 20                                     | 30-86                        | slightly                     | 331   | 199      | 6.3 |
| Fentanyl Citrate       | 3.5mg**                                | 3.7                          | 25                           | 529   | 150      | 8.3 |
| Buprenorphine HCl      | 1.8                                    | 3                            | 12                           | 504   | 209      | 8.5 |

\*\* recommended total high dosage - available only as an injectable for IV and IM use (ref. PDR)

As a practical matter, to be appropriate for transdermal delivery, an analgesic must be therapeutically effective in dosages preferably lower than 50 mg/day. With doses much larger than this, the patch becomes unacceptably large.

- 5 Therefore, many analgesics are inappropriate for transdermal delivery. For example, referring to Table I, the first 7 analgesics listed require daily doses that are too large for practical transdermal delivery. In some instances, however, an analgesic may be a chiral drug (e.g. ketorolac), and thus  
10 when delivered as the active enantiomer the therapeutically effective dose is low enough for transdermal delivery.

- Another consideration in selecting an analgesic for transdermal delivery is that the drug be readily accepted by the skin, thus the drug should be nonirritating,  
15 nonsensitizing and nonmetabolizing. These and other factors that are necessary to consider in selecting a drug to be delivered transdermally are discussed by Flynn et al. Drug Development Research 13:169-185 (1988), incorporated herein by reference.

- 20 The various transdermal formulations and methods of delivery of the present invention are now further illustrated by Examples 1-17 which are exemplary but not scope-limiting. For example, the use of ketorolac tromethamine is used to exemplify matrix patch formulations, however, a matrix design  
25 using ketorolac acid could be formulated without undue experimentation using the methods of the present invention.

#### EXAMPLES OF VARIOUS TRANSDERMAL FORMULATIONS

##### Preparation of ketorolac matrix patches

##### EXAMPLE 1

- 30 Transdermal patches with 10% ketorolac acid were prepared by the following procedure. Ketorolac acid, 0.5 g, was dissolved in 0.21 g of propylene glycol and 0.21 g of isopropyl myristate. This mixture was added to 12.5 g of a pressure sensitive acrylate adhesive solution (34% solids content).  
35 The solution was left to mix for 12 hours on a rolling mill.

The drug-enhancer-adhesive mixture was then cast on Scotchpak X-21220 polyester backing with a 1000  $\mu\text{m}$  casting knife. The solvent in the adhesive solution was evaporated at room temperature for 30 minutes and then in an oven at 100° C for 15 minutes. The resulting adhesive film was laminated to a siliconized release liner (3M #1022). The resulting transdermal patch was cut into disks 5  $\text{cm}^2$  for in vitro evaluation.

The in vitro human skin rates were measured using flow-through diffusion cells (LGA) maintained at 32° C. The receptor fluid, isotonic saline, was pumped into and through the cells by a peristaltic pump. Samples were collected in glass vials arranged in an automatic fraction collector. The human skin was placed on the lower half of the diffusion cell with the stratum corneum facing the donor compartment. The transdermal patch was placed on the stratum corneum and the cumulative amount of ketorolac permeated across the skin ( $\mu\text{g}/\text{cm}^2$ ) was determined by assaying the samples collected by HPLC. The skin flux rate ( $\mu\text{g}/\text{cm}^2 \cdot \text{hr}$ ) was calculated from the cumulative release.

The average flux of ketorolac acid from this patch (10% ketorolac acid, 8% enhancer, and 82% adhesive solids) was  $21.6 \pm 3.59 \mu\text{g}/\text{cm}^2 \cdot \text{hr}$ . The average cumulative amount of ketorolac acid released after 24 hours from these systems was  $461.7 \pm 83.8 \mu\text{g}/\text{cm}^2$ .

#### EXAMPLE 2

Patches were prepared according to the mixing and casting procedure of Example 1 except with the following amounts of components: 0.5 g of ketorolac acid, 0.25 g of propylene glycol, 0.25 g of isopropyl myristate, and 11.7 g of acrylate adhesive 34 wt% solution.

An in vitro flux experiment was conducted following the same procedure outlined in Example 1. The average flux of ketorolac acid from this patch with 10% ketorolac acid, 10%

enhancer, and 80% adhesive solids was  $21.66 \pm 3.07 \mu\text{g}/\text{cm}^2 \cdot \text{hr}$ . The average cumulative amount of ketorolac acid released after 24 hours from these systems was  $324.26 \pm 88.63 \mu\text{g}/\text{cm}^2$ .

### EXAMPLE 3

- 5 Patches were prepared according to the mixing and casting procedure of Example 1 except with the following amounts of components: 0.5 g of ketorolac acid, 0.30 g of propylene glycol, 0.30 g of isopropyl myristate, and 11.4 g of acrylate adhesive 34% solution.
- 10 An in vitro skin flux experiment was conducted following the same procedure outlined in Example 1. The average flux of ketorolac acid from this patch with 10% ketorolac acid, 12% enhancer (propylene glycol/isopropyl myristate), and 78% adhesive solids was  $36.56 \pm 5.35 \mu\text{g}/\text{cm}^2 \cdot \text{hr}$ . The average
- 15 cumulative amount of ketorolac acid released after 24 hours from these systems was  $547.44 \pm 77.23 \mu\text{g}/\text{cm}^2$ .

### EXAMPLE 4

- Patches were prepared according to the mixing and casting procedure of Example 1 except with the following amounts of
- 20 components: 0.52 g of ketorolac acid, 0.21 g of propylene glycol, 0.21 g of isopropyl myristate, and 12.5 g of acrylate adhesive 345 solution.

- An in vitro skin flux experiment was conducted following the same procedure outlined in Example 1. The average flux of
- 25 ketorolac acid from this patch with 10% ketorolac acid, 8% enhancer (propylene glycol/isopropyl myristate), and 82% adhesive solids was approximately  $19.6 \mu\text{g}/\text{cm}^2 \cdot \text{hr}$ . The average cumulative amount of ketorolac acid released after 24 hours from these systems was  $431.27 \pm 149.65 \mu\text{g}/\text{cm}^2$ .

- 30 Preparation of ketorolac monolithic patches

### EXAMPLE 5

Monolithic ketorolac transdermal patches are prepared as follows. A solution of 44% isopropyl alcohol, 22% glycerine,

22% propylene glycol and 12% ketorolac tromethamine is prepared. 11.5 g of the polyurethane prepolymer Hypol 5000 (WR Grace) is weighed into a plastic beaker. 5 g each of the above enhancer drug mixture and of Superfloss Diatomaceous Earth (Celite Corporation) is added to the Hypol 5000. After mixing well the paste is cast between two sheets of siliconized polyester to a thickness of 540  $\mu\text{m}$  on a double roll coater. The matrix is left overnight at room temperature to cure. Disks 5  $\text{cm}^2$  are cut from the matrix, and one side of the siliconized release liner is removed. The exposed matrix is placed on a sample of human skin and the permeation of ketorolac tromethamine is measured as described in Example 1.

#### EXAMPLE 6

A hydrogel-like ketorolac tromethamine transdermal matrix is prepared as follows. 3 g of glycerine and 7 g of deionized water are weighed into a beaker and mixed. 2 g of ketorolac tromethamine is added and mixed until dissolved. 10 g of 2-acrylamido-2-methylpropanesulfonic acid (AMPS, Lubrizol Corporation) is added and mixed. The mixture was purged with argon for 10 minutes while stirring. Then 0.5 g of 0.15% aqueous hydrogen peroxide is added and the prepolymer cast onto Scotchpak X-21220 polyester backing. The prepolymer is cured in the oven at 45°C for 2 hours. After curing, the matrix is rehydrated in the presence of isopropanol, water, and ketorolac tromethamine (44:44:12). Disks 5  $\text{cm}^2$  are cut from the rehydrated matrix, and the permeation of ketorolac tromethamine is measured as described in Example 1.

#### EXAMPLE 7

Ketorolac tromethamine monolithic-type transdermal patches are prepared as follows. First a solution of 24% ketorolac tromethamine, 37% ethanol, 37% water, 1.1% isopropyl myristate and 0.4% hydroxy propyl cellulose is prepared. The matrix of the patch is fabricated by mixing together in a plastic beaker 8 g polyurethane Hypol 2002, 1.4 g water and 10.6 g of the ketorolac solution. The mixture is stirred for 5



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minutes until thickened. After mixing, the paste is cast between two sheets of siliconized polyester to a thickness of 930  $\mu\text{m}$  on a double roll coater. The matrix is cured at 45°C for 5 minutes. Disks with 2.2  $\text{cm}^2$  of active release area are cut from the matrix and one side of the siliconized release liner is removed. The exposed matrix is placed on a sample of human skin and placed on the in vitro test cell. 1 ml of isopropyl alcohol is then placed on the matrix. The permeation of ketorolac tromethamine is measured as described in Example 1.

**Preparation of ketorolac mixed  
monolithic/membrane patches**

**EXAMPLE 8**

Monolithic matrices containing 8.7% ketorolac tromethamine are prepared by the same procedure described in Example 6. Several membranes can be made and laminated to the matrix:

- A. A membrane of 100  $\mu\text{m}$  thick Sclairfilm<sup>®</sup> HD-2-PA is cast onto the monolith.
- B. A 38  $\mu\text{m}$  thick membrane of polyethylene grade HD-106 obtained from Consolidated Thermoplastics is cast onto the monolith.
- C. The membranes of examples A and B are coated with 25- $\mu\text{m}$  thick layer of BIO PSA grade X7-2920.
- D. The monolith is coated with polyethylene, double-sided medical adhesive tape grade 3M-1509.
- E. The monolith is coated with polyethylene, double-sided, medical adhesive tape grade 3M-1512.

**Preparation of ketorolac liquid reservoir patches**

**EXAMPLE 9**

An acrylate adhesive casting solution is prepared including 30% isopropyl myristate. The casting solution is cast onto a polyester film (3M #1022) and dried at room temperature for 30 minutes and then at 100°C for 15 minutes. A nonwoven polyester material is laminated to the resulting adhesive film. This three layer assembly is peripherally heat sealed to polyurethane foam (Foamex Corp.) 1/8 inch in thickness and a backing material, 3M X-21220. The foam reservoir is filled

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with a 24% ketorolac tromethamine solution in 37% ethanol, 37% water, 1.1% isopropyl myristate and 0.4% hydroxy propyl cellulose. The opening in the heat seal by which the fill solution is introduced is sealed after filling and the patches  
5 are tested in vitro as described in Example 1.

## EXAMPLE 10

Reservoir type patches are prepared as in Example 9. In this case, the reservoir is filled with various gelled solution of ketorolac tromethamine. Examples of gelled solutions are:

|                           | A    | B    | C    | D    |
|---------------------------|------|------|------|------|
| 10 Ketorolac tromethamine | 5%   | 10%  | 15%  | 20%  |
| Carbomer                  | 1%   | 1.5% | 1%   | 0.5% |
| Alcohol                   | 20%  | 30%  | 10%  | 50%  |
| 15 EDTA                   | ---  | ---  | ---  | 0.1% |
| BHT                       | 0.1% | ---  | 0.5% | ---  |
| Purified water, q.s. to   | 100% | 100% | 100% | 100% |

The access port for reservoir filling is heat sealed and the  
20 patches are cut to size and packaged in a Barex pouch.

## Preparation of ketorolac carbomer gel

## EXAMPLE 11

Ketorolac tromethamine is dissolved in purified water (about 1/5 of total amount to be prepared). The pH is  
25 adjusted to  $7.3 \pm 0.1$  using NaOH 10% (w/w) solution or trolamine. Alcohol is mixed with 2/3 of the total amount of water and then carbomer is added while stirring. The carbomer is allowed to fully swell for 1 hour at 50° under constant stirring. The remaining NaOH or trolamine is added and  
30 stirred for 15 minutes. The ketorolac solution is joined with the carbomer gel under vacuum and stirred well. The pH is adjusted, if necessary to between 7.3 and 7.5 with NaOH 10% (w/w) solution or trolamine. The remaining purified water is added and stirred for 15 minutes. The gel is collected  
35 in a suitable container and introduced into tubes. The gels have the following composition:

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|                        | A            | B     |
|------------------------|--------------|-------|
| Ketorolac tromethamine | 2%           | 2%    |
| Carbomer               | 1.2%         | 1.2%  |
| Alcohol                | 20%          | 20%   |
| 5 NaOH 5% w/w sol.     | 5%           | --    |
| Trolamine              | --           | 1.94% |
| Purified water         | q.s. to 100% | 100%  |

### Preparation of ketorolac hydroxyethylcellulose gel

#### EXAMPLE 12

10 Ketorolac tromethamine is dissolved in purified water (about 1/5 of total amount to be prepared). The pH is adjusted to  $7.3 \pm 0.1$  using 1N NaOH. Alcohol is mixed with 2/3 of the total amount of water and then hydroxyethylcellulose is added while stirring. The

15 hydroxyethylcellulose is allowed to fully swell for 1 hour at 50° under constant stirring. The remaining NaOH is added and stirred for 15 minutes. The ketorolac solution is joined with the hydroxyethylcellulose gel under vacuum and stirred well. The pH is adjusted, if necessary to between 7.3 and

20 7.5 with NaOH. The remaining purified water is added and stirred for 15 minutes. The gel is collected in a suitable container and introduced into tubes. When present, sodium edetate has been solubilized together with ketorolac. The gels have the following composition:

|                           | A            | B     |
|---------------------------|--------------|-------|
| 25 Ketorolac tromethamine | 1%           | 1%    |
| Hydroxyethylcellulose     | 2%           | 2%    |
| Alcohol                   | 20%          | 20%   |
| NaOH 1N sol.              | --           | 1.15% |
| 30 Sodium edetate         | --           | 0.5%  |
| Purified water            | q.s. to 100% | 100%  |

### Preparation of fentanyl transdermal patch

#### EXAMPLE 13

Transdermal patches are prepared by adding 15 mg/g of fentanyl

35 base to a 30% ethanol-water solvent. The solution is gelled with 1% hydroxypropyl cellulose by adding the gelling agent slowly with stirring and then mixing for 2 hours. A pressure sensitive contact adhesive is prepared by casting the adhesive

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solution into a siliconized release liner with a 1000  $\mu\text{m}$  casting knife. After solvent evaporation, an adhesive film 100  $\mu\text{m}$  in thickness is formed. Cotran microporous polyethylene membrane is then laminated to the adhesive film.

5 A backing material, Scotchpak 1009, is peripherally heat sealed to the Cotran/adhesive/release liner laminate to form patches 5  $\text{cm}^2$  in area. The patch reservoir is filled with the gelled fentanyl base solution. The access port for reservoir filling is heat sealed and the patches are pouched

10 and allowed to equilibrate. After 1 week equilibration the in vitro release of fentanyl base is measured through human skin.

#### Preparation of methadone transdermal patch

##### EXAMPLE 14

15 Transdermal patches are prepared as in Example 14 except the fill solution is a saturated solution of methadone base in 50% ethanol:water solvent. The methadone:ethanol:water mixture is gelled with 1% Carbopol 934P. The patches are filled with the methadone solution, left pouched for 1 week

20 to equilibrate and then tested in vitro.

#### Preparation of buprenorphine transdermal patch

##### EXAMPLE 15

A transdermal patch for delivery of buprenorphine is prepared by the following procedure. A solution of 80% propylene glycol and 20% lauryl alcohol is prepared. Buprenorphine

25 Hydrochloride is added to the mixture to saturation and placed on a double roll mill until homogenous. The drug plus enhancer mixture is added to a solvent based acrylate adhesive casting solution to a loading level of 20%. The adhesive

30 formulation is cast onto a siliconized release liner (3M #1022) with a 1000  $\mu\text{m}$  casting bar. The solvent in the adhesive solution is allowed to evaporate, first at room temperature for 30 minutes and then in an oven at 100° C for 15 minutes. A clear, impermeable backing material is

35 laminated to the drug and enhancer loaded adhesive film.

Transdermal patches of the desired size are punched from the laminate and tested in vitro.

#### Nasal Drug Delivery

- For systemic drug administration, the nasal route appears to be an ideal alternative to the use of parenterals, especially in view of the rich supply of blood vessels in the nasal mucosa, which greatly enhances drug absorption, and the ease of intranasal drug delivery. In addition, there are other advantages that are achieved through nasal delivery. First, the nasal route avoids hepatic "first-pass" elimination, gut wall metabolism, and/or destruction in the gastrointestinal tract. Another benefit is that the rapid rate of absorption as well as the high plasma concentrations obtained are comparable to those obtained by intravenous medication.
- For the nasal delivery of analgesics to be effective in the treatment of incident pain, it is desirable that the drug administered is rapidly and thoroughly absorbed, giving therapeutic effects equivalent to those obtained by the intravenous route or the intramuscular or oral routes, without inducing severe side effects. The molecular size and pKa of the analgesic are some of the physico-chemical properties that should be considered in selecting a drug for nasal delivery. Nasal absorption is pH dependent with absorption being greater at pH levels below pKa. In general, nasal absorption decreases as pH increases owing to ionization of the penetrant molecule. In addition, the pH of the drug delivery vehicle is also important. As with transdermal delivery, for practical nasal delivery, an analgesic must be therapeutically effective in dosages preferably lower than 50 mg/day.
- Another consideration is the half-life of the analgesic. The half-life of a drug is the amount of time it takes the total level of drug in a body to decrease by 50%. Since, given the teachings of the present invention, the purpose of nasal delivery is to rapidly increase levels of analgesic above base-line level for relief of incident pain, it is preferable

to deliver a drug that will provide relief when needed, but not result in a prolonged increase in blood levels of analgesic long after incident pain has subsided. Thus it is preferable that the analgesic delivered nasally has a half-life of less than 6 hours, and more preferably less than 4 hours.

A preferred analgesic that can be effectively administered by the nasal route is ketorolac. While nasal delivery can be accomplished using a gel or a suspension as a vehicle, the delivery of ketorolac is preferably in the form of a solution which may be delivered by drops, or as a spray using atomizers equipped with a mechanical valve and possibly including a propellant of a type commercially available. Vehicles suitable for spray administration are water, alcohol, glycol and propylene glycol, used alone or in a mixture of two or more.

Generally, illustrative formulations of ketorolac solution for nasal delivery will contain the following ingredients and amounts (weight/volume):

| <u>Ingredient</u>       | <u>Broad Range (%)</u> | <u>Preferred Range (%)</u> |
|-------------------------|------------------------|----------------------------|
| Na <sub>2</sub> EDTA    | 0.001 - 1              | 0.05 - 0.1                 |
| Nipagin                 | 0.01 - 2               | 0.05 - 0.29                |
| POE(9) Lauryl alcohol   | 0.1 - 10               | 1 - 10                     |
| NaCMC (Blanose 7m8 sfd) |                        | 0.3 - 3                    |
| Carbopol 940            | 0.05 - 2               | 0.1 - 1.5                  |
| Glycerol                | 1 - 99                 |                            |
| Sodium glycocholate     | 0.05 - 5               | 0.1 - 1                    |

It will be appreciated by those of ordinary skill that ingredients such as sodium carboxymethyl cellulose and Carbopol exist in many types that differ in viscosity. Their amounts are to be adjusted accordingly. Different adjustments to each formulation may also be necessary including omission of some optional ingredients and addition of others. It is

thus not possible to give an all-encompassing amount range for each ingredient, but the optimization of each preparation according to the invention is within the skill of the art.

- An alternative formulation for the nasal delivery of ketorolac comprises a suspension of finely micronized active ingredient (generally from 1 to 200 micrometers, preferably from 5 to 100 micrometers) in a propellant or in an oily vehicle or in another vehicle in which the drug is not soluble. The vehicle is mixed or emulsified with the propellant. Vehicles suitable for this alternative are, for instance, vegetable and mineral oils and triglyceride mixtures. Appropriate surfactants, suspending agents and diluents suitable for use in pharmaceuticals are added to these vehicles. Surfactants include, without limitation, sorbitan sesquioleate, sorbitan monooleate, sorbitan trioleate (between about 0.25 and about 1%). Suspending agents include, without limitation, isopropylmyristate (between about 0.1 and about 0.5%); and diluents include, without limitation, zinc stearate (about 0.6 to about 1%).
- The various nasal formulations of the present invention are now further illustrated by Examples 16-25 which are exemplary but not scope-limiting.

#### EXAMPLES OF VARIOUS NASAL FORMULATIONS

##### Ketorolac Nasal Spray Formulations

|    |                                 | <u>EXAMPLE 16</u> |                      |
|----|---------------------------------|-------------------|----------------------|
|    |                                 | <u>%</u>          | <u>For 10 liters</u> |
| 25 | <u>Composition</u>              |                   |                      |
|    | Ketorolac tromethamine          | 5                 | 500 g                |
|    | EDTA disodium (chelating agent) | 0.01              | 1 g                  |
|    | NIPAGIN (preservative)          | 0.1               | 10 g                 |
| 30 | Purified water, q.s. to         | 100               | 10 L                 |

##### Method of Preparation

In a suitable vessel equipped with mixer and heating sleeve, introduce about 9 liters of purified water and heat to a temperature of 80°C. Dissolve NIPAGIN and EDTA disodium.

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Stir the solution constantly to complete dissolution of the components. Cool the resulting solution to room temperature. Dissolve ketorolac tromethamine by stirring. Bring to volume with water. The isotonicity of this composition was 190 mOsm but can be adjusted e.g. to 270 mOsm by the addition of 0.3% NaCl or 2.03% glucose.

**EXAMPLE 17**

|    | <u>Composition</u>                            | <u>%</u> | <u>For 10 liters</u> |
|----|---|----------|----------------------|
|    | Ketorolac tromethamine                        | 5        | 500 g                |
| 10 | POE (9) lauryl alcohol<br>(enhancer/promoter) | 5        | 500 g                |
|    | NIPAGIN                                       | 0.1      | 10 g                 |
|    | EDTA disodium                                 | 0.01     | 1 g                  |
|    | Purified water, q.s. to                       | 100      | 10 L                 |

**15 Method of Preparation**

In a suitable vessel equipped with mixer and heating sleeve, introduce about 9 liters of purified water and heat to a temperature of 80°C. Dissolve NIPAGIN and EDTA disodium. Stir the solution constantly to complete dissolution of the components. Cool the resulting solution to room temperature. Add POE (9) lauryl alcohol and stir to complete dissolution. Dissolve ketorolac tromethamine by stirring. Bring to volume with water.

**EXAMPLE 18**

|    | <u>Composition</u>             | <u>%</u> | <u>For 10 liters</u> |
|----|--------------------------------|----------|----------------------|
| 25 | Ketorolac tromethamine         | 5        | 500 g                |
|    | Sodium carboxymethyl cellulose | 1        | 100 g                |
|    | Tromethamine, q.s. to pH = 6   |          |                      |
|    | NIPAGIN                        | 0.1      | 10 g                 |
| 30 | Purified water, q.s. to        | 100      | 10 L                 |

**Method of Preparation**

In a suitable vessel equipped with mixer and heating sleeve, introduce about 9 liters of purified water and heat to a temperature of 80°C. Dissolve NIPAGIN. Cool the obtained solution to room temperature. Dissolve ketorolac tromethamine



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and continue stirring to complete dissolution of the drug. Disperse sodium carboxymethyl cellulose in the solution stirring vigorously. Continue stirring to complete hydration of the polymer. Adjust the pH to the required value by adding tromethamine dissolved in water. Bring to volume with water.

## EXAMPLE 19

| <u>Composition</u>               |      | <u>%</u> | <u>For 10 liters</u> |
|----------------------------------|------|----------|----------------------|
| Ketorolac tromethamine           |      | 5        | 500 g NIPAGIN        |
| 0.1                              | 10 g |          |                      |
| 10 EDTA disodium                 |      | 0.01     | 1 g                  |
| CARBOPOL 940                     |      | 0.1      | 10 g                 |
| Tromethamine, q.s. to pH = 7-7.4 |      |          |                      |
| Glycerol                         |      | 2        | 200 g                |
| Purified water, q.s. to          |      | 100      | 10 L                 |

15 Method of Preparation

In a suitable vessel equipped with mixer and heating sleeve, introduce about 4 liters of purified water and heat to a temperature of 80°C. Dissolve NIPAGIN and EDTA. Cool the solution to room temperature. Dissolve ketorolac tromethamine and continue stirring to complete dissolution of the drug. Adjust the pH to the required value by adding tromethamine dissolved in water. In a separate vessel equipped with a mixer, add the glycerol. Introduce CARBOPOL and mix until a homogeneous dispersion in the glycerol is obtained. Add 4 liters of purified water with vigorous stirring and continue stirring the solution to complete hydration of the polymer. Combine the ketorolac solution and the polymer solution while stirring. If necessary, adjust the pH to the required value with the tromethamine solution. Bring to volume with water.

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## EXAMPLE 20

|   | <u>Composition</u>      | <u>%</u> | <u>For 10 liters</u> |
|---|-------------------------|----------|----------------------|
|   | Ketorolac tromethamine  | 5        | 500 g                |
|   | LUTROL F127             | 17       | 1.7 Kg               |
| 5 | EDTA disodium           | 0.01     | 1 g                  |
|   | NIPAGIN                 | 0.1      | 10 g                 |
|   | Purified water, q.s: to | 100      | 10 L                 |

Method of Preparation

- In a suitable vessel equipped with mixer and heating sleeve,  
10 introduce about 4 liters of purified water and heat to a temperature of 80°C. Dissolve NIPAGIN and EDTA disodium. Cool the solution to 4°C and, while maintaining the solution between 4 and 6°C, gradually add Lutrol F127 while stirring. Continue stirring to complete hydration of the polymer. Cool  
15 the resulting solution to room temperature. Bring the solution to room temperature. Dissolve ketorolac tromethamine by stirring. Bring to volume with water.

## EXAMPLE 21

|    | <u>Composition</u>             | <u>%</u> | <u>For 10 liters</u> |
|----|--------------------------------|----------|----------------------|
| 20 | Ketorolac tromethamine         | 5        | 500 g                |
|    | Sodium carboxymethyl cellulose | 2        | 200 g                |
|    | EDTA disodium                  | 0.01     | 1 g                  |
|    | NIPAGIN                        | 0.1      | 10 g                 |
|    | Purified water, q.s. to        | 100      | 10 L                 |

- 25 The procedure of Example 19 was used to make the above formulation except that no buffer was added.

## EXAMPLE 22

|    | <u>Composition</u>              | <u>%</u> | <u>For 10 liters</u> |
|----|---------------------------------|----------|----------------------|
|    | Ketorolac tromethamine          | 5        | 500 g                |
| 30 | EDTA disodium (chelating agent) | 0.01     | 1 g                  |
|    | NIPAGIN (preservative)          | 0.1      | 10 g                 |
|    | Sodium glycocholate             | 0.3      | 30 g                 |
|    | Purified water, q.s. to         | 100      | 10 L                 |

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The procedure of Example 17 was used except that sodium glycocholate was dissolved with the nipagin and disodium EDTA at 80° in water. The isotonicity of this composition was 190 mOsm; it can be adjusted e.g. to 330 mOsm by the addition of 5 0.44% NaCl or 3.05% glucose.

**EXAMPLE 23**

| <u>Composition</u>      | <u>%</u> | <u>For 10 liters</u> |
|-------------------------|----------|----------------------|
| Ketorolac tromethamine  | 5        | 500 g                |
| LUTROL F127             | 15       | 1500 g               |
| 10 Sodium glycocholate  | 0.3      | 30 g                 |
| EDTA disodium           | 0.01     | 1 g                  |
| NIPAGIN                 | 0.1      | 10 g                 |
| Purified water, q.s. to | 100      | 10 L.                |

The procedure of Example 23 was used except that sodium 15 glycocholate was dissolved along with nipagin and disodium EDTA at 80°C.

**Morphine nasal spray formulation****EXAMPLE 24**

| <u>Composition</u>            | <u>%</u> |
|-------------------------------|----------|
| 20 Morphine sulphate          | 5%       |
| Sodium carboxymethylcellulose | 1%       |
| Water q.s. to                 | 100%     |

Method of preparation

50 grams morphine sulfate is dissolved in 800 ml purified 25 water and pH adjusted to 6.5. Sodium carboxymethylcellulose is dispersed in the solution and stirred vigorously until there is complete hydration of the polymer. A quantity of distilled water, sufficient to bring the total volume to 1 liter is then added.

30

**Fentanyl nasal spray formulation****EXAMPLE 25**

100 grams fentanyl citrate is dissolved in 800 ml of purified water and the pH of the obtained solution is adjusted to pH 6. Water is then added to bring the total volume to 1 liter. Sufficient sodium chloride can be added to adjust the solution to isotonicity. 5 grams of sodium glycocholate is added. The final solution contains 10 mg of fentanyl in 100  $\mu$ l of solution.

#### Combined Transdermal/Nasal Delivery

Patients experiencing a baseline level of pain can achieve sufficient analgesia with a transdermal device which maintains a baseline level of drug in the body. For bouts of incident pain that commonly occur in patients with a pain condition, such as when they get up in the morning or when they perform an activity requiring movement, a nasal dose of a rapidly acting analgesia would provide relief. Typically a nasal dose would be one spray of analgesic up each nostril, each spray having about 100  $\mu$ l analgesic solution. Nasal delivery gives peak blood levels within 10-15 minutes and would effectively handle the stress and pain associated with activities or moments that instigate incident pain.

Given the teachings of the present invention, the patient with a pain condition has available, the nasal delivery of analgesia, thus enabling the patient to perform activities that would otherwise be painful. Typically, a combination of 2-7 doses of nasal analgesia with a continuously delivering transdermal device will beneficially aid the patient through the day. During the night, the transdermal patch maintains a baseline blood level, but as no nasal doses are taken while the patient sleeps, there is a washout period for the neuro-receptors. Thus, this regimen throughout the day and night effectively and easily achieves the pulsatile delivery that reduces the problem of tolerance.

The combined delivery of nasal and transdermal drug delivery generally is best if the drug delivered nasally has a short half-life of less than 6 hours, preferably less than 4 hours.

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- A short half-life better enables the pulsatile delivery regimen that most effectively manages the pain condition experienced by patients. This is because blood levels more rapidly return to baseline provided by the transdermal patch so that there are periods of washout between nasal doses. Since a washout period is desirable, the patient should avoid taking more than about 3-5 doses at a given time for two reasons: (1) increased likelihood of irritation and (2) higher overall blood levels rather than pulsed delivery.
- 10 For effective pain management, it is not necessary that the nasal doses be spaced regularly throughout the day. Many patients will take a dose only as needed in response to pain. Typically, the patient would take a nasal dose of analgesia in the morning when getting out of bed and may take a second
- 15 dose relatively soon thereafter - in 30 minutes to 1 or 2 hours. Then no more nasal doses may be needed for several hours. At some point during the day, nasal doses may be taken at widely spaced intervals or, alternatively, two nasal doses close together may be taken. Other patients may only require
- 20 nasal doses before engaging in certain activities.

Although it will be clear to those skilled in the art that many analgesic drugs can be formulated into useful combinations of transdermal and nasal formulations, we have found that a preferred class of formulations are those

25 incorporating the drugs ketorolac, fentanyl, methadone, morphine, and buprenorphine. Of these drugs, ketorolac is a non-narcotic analgesic, and the others are narcotic analgesics.

A preferred method for the management of pain conditions therefore is a combination of nasal or transdermal delivery

30 of ketorolac and then nasal or transdermal delivery of a narcotic analgesic. Even more preferably, ketorolac is delivered transdermally and one of the narcotic analgesics is delivered nasally. For example, ketorolac may be delivered

35 transdermally, while fentanyl is delivered nasally.

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Alternatively, morphine or buprenorphine could be administered nasally in place of the fentanyl. Each of these narcotics has a short half-life, in the range of 2 to 4 hours. Thus an ideal method of pain management would be constant  
5 transdermal delivery of a non-narcotic analgesic for 24-hour periods, with nasal administration of a narcotic analgesic 3 to 4 times per day with an 8 hour wash out period during the night when no drug is delivered nasally. In this way, the transdermal ketorolac formulation, such as one of the  
10 types described in Examples 9 or 10 above, can deliver 20-50 mg/day of ketorolac to provide a base level of analgesia throughout a 24 hour period.

As the need arises, the patient can treat any incident pain associated with movement, eating meals, etc., by periodically  
15 using a nasal formulation, such as those described in Examples 24 and 25. These short acting but powerful narcotic drugs, when delivered nasally, will produce rapid relief because of their rapid adsorption through the nasal mucosa, yet avoid the problems of tolerance and dependence because their short  
20 half-lives allow the drugs to essentially completely eliminate from the body during sleep. A particular advantage of this therapy is that because a combination of narcotic and non-narcotic analgesics is used, which work on different types of pain receptors, a more pronounced analgesia is obtained.

25 It follows from the above discussions that the combination of transdermal ketorolac with nasal delivery of the narcotic methadone, should be a less preferred combination because of the long half-life of methadone. When delivered nasally 2 or 4 times per day or more, methadone would accumulate in the  
30 body and gradually lose its effect due to tolerance. Dependence to the drug would also be a concern.

Although the delivery of a non-narcotic analgesic transdermally combined with the delivery of a narcotic analgesic having a short half-life is preferred, another very  
35 desirable combination is the delivery of one non-narcotic

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analgesic transdermally and another non-narcotic analgesic nasally, or the same non-narcotic analgesic delivered both nasally and transdermally. For example, ketorolac could be delivered transdermally using devices such as those described in Examples 1-10 to achieve baseline analgesia, while a nasal formulation of ketorolac, such as those described in Examples 16-23, is used to treat incident pain. This is a preferred combination because ketorolac and similar non-narcotic analgesics can be prescribed by physicians without fear of diversion to drugs of abuse or danger of inducing narcotic drug dependency in the patient.

Finally, because some patients respond better to narcotic analgesics, the combination of a narcotic analgesic delivered transdermally and a non-narcotic analgesic delivered nasally would be desirable with these patients. For example, a fentanyl transdermal patch can be worn to alleviate baseline pain, while ketorolac could be delivered nasally to relieve bouts of incident pain. Alternatively, a methadone patch could be worn to achieve baseline analgesia while ketorolac is delivered nasally as needed for the treatment of incident pain.

For the management of more severe pain, or for the control of pain of patients who don't respond to non-narcotic analgesics such as ketorolac, the transdermal delivery of fentanyl or methadone could be combined with the nasal delivery of formulations of fentanyl or morphine, such as those described in Examples 25 and 26. This powerful combination of narcotic drugs would be best suited for hospital use, for example, for the treatment of post-operative pain. Patients who respond more effectively to the narcotic type analgesics will maintain a level of comfort for baseline pain with the narcotic transdermal patch. Periodic doses of the narcotic analgesic nasal spray will relieve incident pain. This combination delivery mode is likely to result in overall lower blood levels and therefore fewer side effects when compared to conventional injection and oral dosage forms.

The method of combined transdermal and nasal delivery of analgesics as taught by the present invention is now further illustrated by Example 26 which is exemplary but not scope-limiting. Methods for the testing of in vivo release of analgesics are set forth in Examples 28 and 29.

**EXAMPLES OF COMBINED TRANSDERMAL AND NASAL  
DELIVERY OF ANALGESICS**

**Ketorolac transdermal and ketorolac nasal**

**EXAMPLE 26**

10        Ten patients undergoing surgery involving an abdominal incision are given a nasal dose of 2 sprays up each nostril of 100  $\mu$ l/spray 5% ketorolac tromethamine solution. Subsequently, a transdermal patch of ketorolac as described in Example 1 is applied to a non-hairy area of the upper  
15    anterior chest wall of each patient (alternatively, other patch formulations can be used, such as those described in Examples 3-10). This combined use of transdermal and nasal drug delivery methods is based on the consideration that there may be a delay of at least one hour before therapeutically  
20    effective concentrations from a transdermal system can be reached. The patch remains in situ for 24 hours and is then removed. A new patch is applied to the identical site on the contralateral side and is left in place for a further 24 hours. The transdermal ketorolac dose for the second 24 hour  
25    period is kept the same or either increased if analgesia was inadequate or decreased by using a smaller patch if the patient exhibits signs of toxicity. For supplementary pain relief, additional analgesia is administered nasally.

**In vivo release of ketorolac tromethamine**

**EXAMPLE 27**

30        Transdermal patches are prepared as in Example 7 except with an active release area of 20 cm<sup>2</sup>. The patches are placed on the abdominal area of four volunteers and left in place for 24 hours. Three milliliter blood samples are taken at  
35    appropriate intervals over a 24 hour period and analyzed for ketorolac content. After a 4 hour lag time the blood plasma



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concentration of ketorolac is 0.45  $\mu\text{g/ml}$ , a therapeutically effective level for baseline analgesia. The blood level remains relatively constant for 24 hours at which time the patch is removed and a fresh patch placed again on the abdominal area. During this second 24 hour period, each subject administers a dose of the nasal spray described in Example 16 every 4 hours. A dose (one spray up each nostril) of the nasal spray will deliver approximately 1  $\mu\text{g/ml}$  of ketorolac. Three milliliter blood samples are taken at regular intervals and blood plasma levels rise to 1  $\mu\text{g/ml}$  after nasal administration and then decline to the baseline of 0.45  $\mu\text{g/ml}$  for the interval between nasal doses.

#### In vivo release of fentanyl

##### EXAMPLE 28

Fentanyl transdermal patches prepared as in Example 12 are placed on the abdomen of a volunteer. Blood samples are taken at two hour intervals for 10 hours at which time the blood concentration is constant at 0.76 ng/ml, a therapeutically effective level for baseline analgesia. The volunteer then takes a dose from the ketorolac nasal spray prepared as in Example 14 and a blood sample is withdrawn every 15 minutes for a 1 hour period. The blood sample is assayed for ketorolac and for fentanyl. The fentanyl concentration remains at 0.78 ng/ml while the ketorolac concentration spikes 30 minutes after the delivery of the nasal spray. Four hours after the first nasal dose, another dose is taken and the blood level again monitored. A spike of ketorolac in the blood occurs.

#### Iontophoresis

Many pharmacologically-active agents or drugs have the ability to exist in the ionized state depending on the pH of the surrounding environment. In terms of topical delivery, ionization at the skin surface normally results in a low transport rate for an applied drug. However, the use of iontophoresis enhances the local delivery of topically-applied

agents as well as improves the systemic delivery of the drug into the bloodstream. In the simplest situation, the drug is placed in an electrode compartment and adjusted to a pH whereby the molecules have the same net charge as the electrode. A return electrode, having an opposite charge, is also placed somewhere on the skin distal from the drug electrode. It has also been shown that in studies with neutral molecules, their transport is also enhanced with the use of iontophoresis. This effect is due to the electroosmotic flow of water through the skin which normally occurs from the anode to the cathode (R. Burnette, J. Pharm. Sci., 75:738 (1986)).

There are several approaches which can be used to further improve or optimize the result of iontophoresis. These include the use of chemical enhancers in conjunction with iontophoresis. It has been shown, for example, that the coapplication of oleic acid to the skin causes a large decrease in the skin impedance or resistance which is inversely related to permeability or transport (Potts et al, Solid State Ionics, 53-56: 165-169, (1992)). In addition, variations in the magnitude and duration of the electric potential may have some advantages.

Formulations for iontophoretic use are usually optimized with respect to drug concentration, pH, presence of enhancers or solvents other than water, ionic strength, as well as buffer type and concentration. In general, these parameters are varied to maximize the efficiency of electromotive transport for the drug. For example, the pH would normally be adjusted to insure that the drug is fully ionized and the buffer type would possess an opposite charge so as not to compete or contribute to the ionic current across the skin. Solvents and ionic strength can have profound effects on the efficiency of transport and, therefore, need to be adjusted accordingly. In some cases, an enhancer or nonaqueous cosolvent such as ethanol may be added to improve the transport or vary the route of permeation.

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The analgesics which would be most preferable for delivery by iontophoresis would be those which can be ionized with a positive charge (since the skin is permselective for cations) and which have a high solubility in the applied formulation.

5 Further, if iontophoresis was being utilized to treat incident pain, it would be preferable to employ those analgesics that have short half-lives.

Iontophoresis can be used to treat both base-line and incident pain. When used to treat base-line pain, a low-current

10 iontophoresis device can be used. The term "low-current iontophoresis device" as used herein refers to devices that deliver a current in the range of 0.02-1.0 mAmp/cm<sup>2</sup>. To treat incident pain, a high-current iontophoresis device can be used. The term "high-current iontophoresis device" as used

15 herein refers to devices that deliver a current in the range of 0.5-5mAmp. It will be appreciated that a low-current iontophoresis device that is being used to provide relief from base-line pain could be designed so as to allow for increased current upon patient demand and need and thus temporarily act

20 as a high-current iontophoresis device.

#### EXAMPLES OF VARIOUS IONTOPHORETIC FORMULATIONS

##### Piroxicam Iontophoretic Formulation

##### EXAMPLE 29

|    | <u>Composition</u>     | <u>%</u> |
|----|------------------------|----------|
| 25 | Piroxicam              | 0.5      |
|    | Hydroxyethyl cellulose | 0.4      |
|    | Ethanol                | 1.3      |
|    | Propylene glycol       | 42.0     |
|    | Benzyl alcohol         | 20.0     |
| 30 | Triethanolamine        | 2.0      |
|    | Water, qs to           | 100      |

pH adjusted to 7-7.5 with triethanolamine.

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**Morphine Iontophoretic Formulation****EXAMPLE 30**

| <u>Composition</u>        | <u>%</u> |
|---------------------------|----------|
| Morphine                  | 0.1-5    |
| 5 Sodium chloride         | 0.9      |
| Water, qs to              | 100      |
| pH adjust to 3-4 with HCl |          |

**Ketorolac Tromethamine Iontophoretic Formulation****EXAMPLE 31**

|    |                                   |          |
|----|-----------------------------------|----------|
| 10 | <u>Composition</u>                | <u>%</u> |
|    | Ketorolac tromethamine            | 0.1-5    |
|    | Ethanol                           | 10.0     |
|    | Sodium chloride                   | 0.7      |
|    | Water, qs to                      | 100      |
| 15 | pH adjust to 5-7 with NaOH or HCl |          |

**Fentanyl Citrate Iontophoretic Formulation****EXAMPLE 32**

| <u>Composition</u>                | <u>%</u>  |
|-----------------------------------|-----------|
| Fentanyl citrate                  | 0.005-0.1 |
| 20 Ethanol                        | 10.0      |
| Water, qs to                      | 100       |
| pH adjust to 4-6 with NaOH or HCl |           |

**Combined Iontophoresis and Transdermal or Nasal Delivery Systems**

- 25 Patients experiencing a baseline level of pain can achieve sufficient analgesia with a transdermal patch device which maintains a baseline level of drug in the body. For bouts of incident pain that commonly occur in patients with a pain condition, such as when they get up in the morning or when
- 30 they perform an activity requiring movement, a dose of analgesic administered by a high-current iontophoretic system would provide rapid relief. High-current iontophoresis is particularly beneficial for the treatment of incident pain

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that is localized in a particular area such as a joint. In such a situation, the iontophoresis device may be directly administered to the site of pain. For example, an analgesic may be delivered directly at the site of inflammation. For  
5 a review of iontophoresis and iontophoretic devices, see Tyle, Pharm. Res., 3:318-326 (1986), which is incorporated herein by reference.

Alternatively, a low-current iontophoresis device can be used to achieve a base-line level of analgesia while a nasal  
10 formulation or a high-current iontophoretic system is used to provide relief from incident pain. Generally, the low-current iontophoretic system should be applied at a site that is well supplied with blood vessels so that the analgesic delivered readily reaches the blood stream to provide relief  
15 from base-line pain.

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## WHAT IS CLAIMED IS:

1. A method of providing pain relief said method comprising:
  - (a) administering an analgesic to a person in need of pain relief through a first drug delivery means to provide a continuous base-line level of analgesic, and
  - (b) administering an analgesic to said person through a second drug delivery means to periodically and temporarily increase levels of analgesic above said base-line level.
2. The method of Claim 1 wherein said first drug delivery means is transdermal patch.
3. The method of Claim 1 wherein said first drug delivery means is a low-current iontophoresis device.
4. The method of Claim 1 wherein said second drug delivery means is a nasal formulation delivery device.
5. The method of Claim 1 wherein said second drug delivery means is a high-current iontophoresis device.
6. The method of Claim 1 wherein said base-line level of analgesia is achieved for 12 hours or more.
7. The method of Claim 1 wherein said first analgesic is selected from the group consisting of ketorolac, fentanyl, methadone, morphine and buprenorphine.
8. The method of Claim 1 wherein said analgesic delivered by said first drug delivery means is the same as said analgesic delivered by said second drug delivery means.
9. The method of Claim 8 wherein the analgesic is ketorolac.

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10. The method of Claim 1 wherein said analgesic delivered by said first drug delivery means is different than said analgesic delivered by said second drug delivery means.

11. The method of Claim 1 wherein said second drug  
5 delivery means delivers an amount of analgesic that is therapeutically effective in relieving incident pain.

12. The method of Claim 1 wherein said second drug delivery means increases levels of analgesic above said base-line level within 30 minutes after administration.

10 13. The method of Claim 1 wherein said second drug delivery means delivers an analgesic selected from the group consisting of ketorolac, fentanyl, methadone, morphine, and buprenorphine.

14. The method of Claim 1 wherein said analgesic  
15 delivered by said second drug delivery means has a half-life of less than about 6 hours.

15. The method of Claim 1 wherein said analgesic delivered by said second drug delivery means has a half-life of less than about 4 hours.

20 16. The method of Claim 1 wherein said first drug delivery means is a transdermal patch that delivers less than about 50 mg/day of ketorolac.

17. The method of Claim 1 wherein said second analgesic is selected from the group consisting of ketorolac, fentanyl,  
25 methadone, morphine, and buprenorphine.

18. The method of Claim 17 wherein said second analgesic is ketorolac.

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19. The method of Claim 18 wherein the ketorolac is delivered by the nasal administration of a formulation having about 100  $\mu$ l/spray of about a 5% ketorolac solution.

20. The method of Claim 1 wherein said first analgesic  
5 is a non-narcotic analgesic and said second analgesic is a narcotic analgesic.

21. The method of Claim 20 wherein said first analgesic is ketorolac, and said second analgesic is selected from the group consisting of morphine, fentanyl, and buprenorphine.

10 22. The method of Claim 1 wherein said first analgesic is a narcotic analgesic and said second analgesic is a non-narcotic analgesic.

23. The method of Claim 22 wherein said first analgesic is selected from the group consisting of fentanyl and  
15 methadone and said second analgesic is ketorolac.

24. The method of Claim 1 wherein said first analgesic and said second analgesic are non-narcotic analgesics.

25. The method of Claim 1 wherein said first analgesic and said second analgesic are narcotic analgesics.



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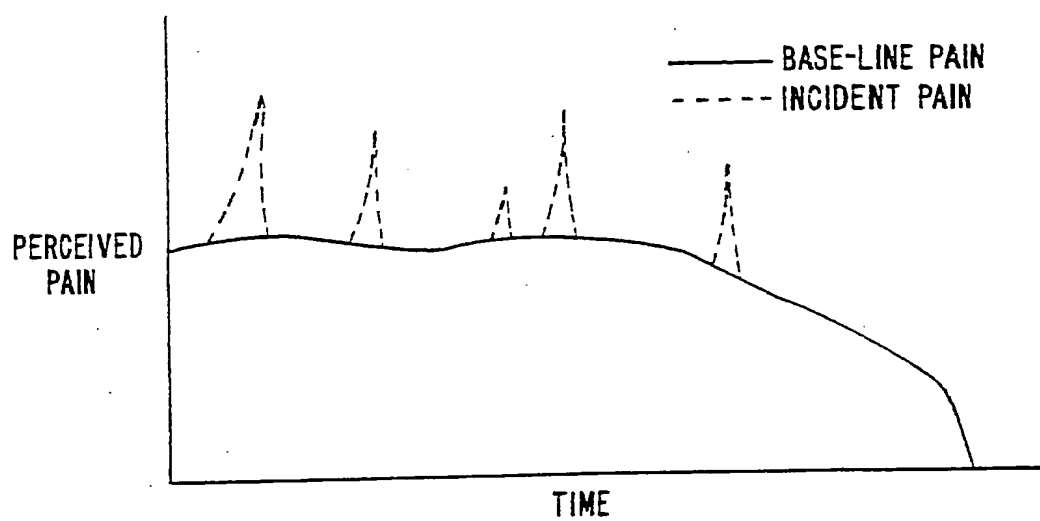


FIG. 1.

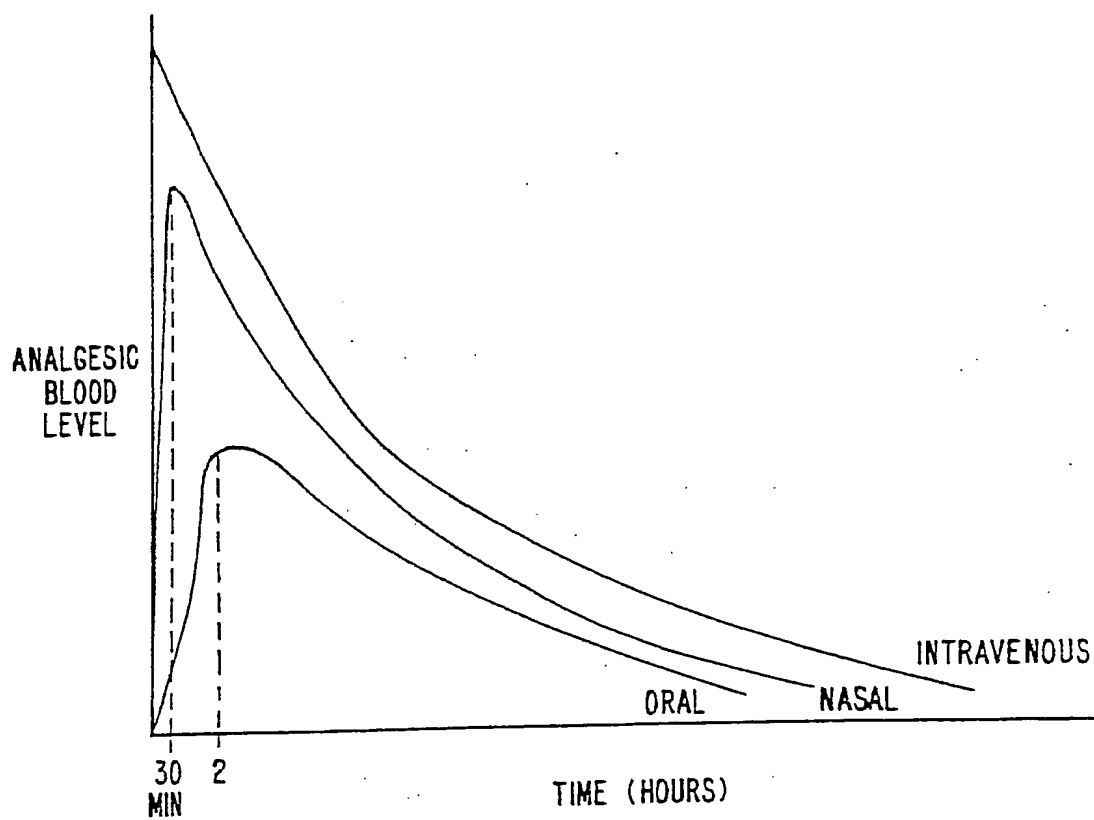


FIG. 2A.

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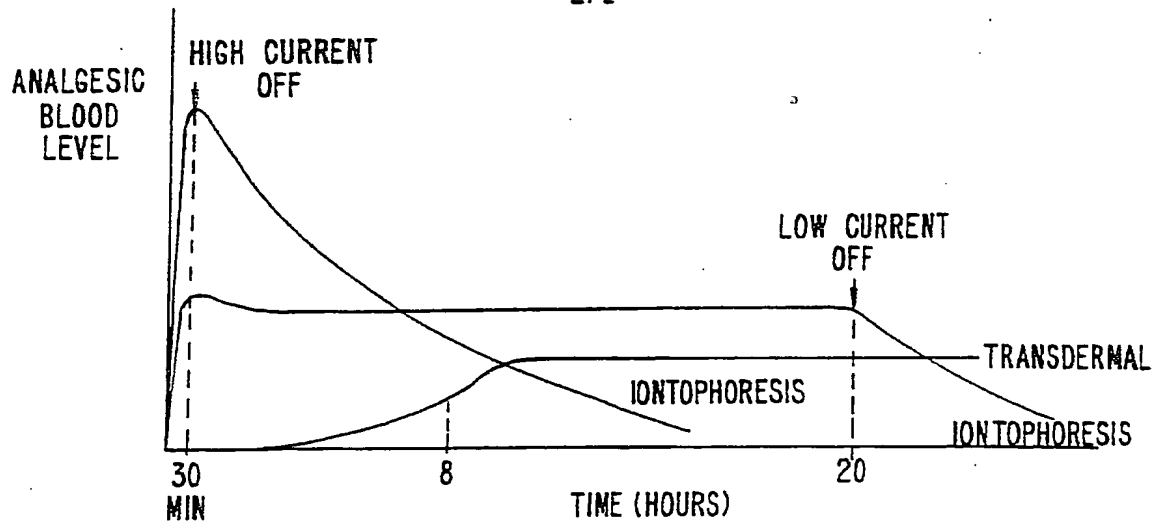


FIG. 2B.

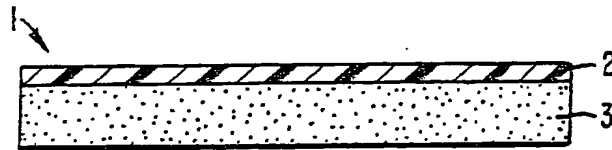


FIG. 3.

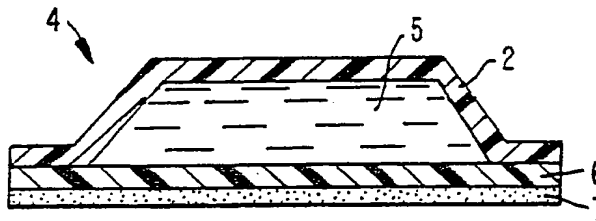


FIG. 4.

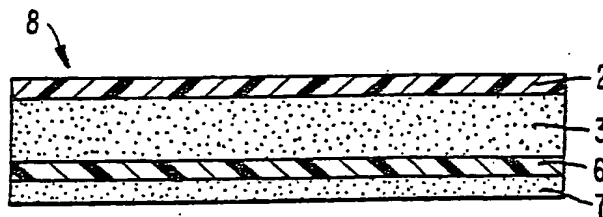


FIG. 5.

## INTERNATIONAL SEARCH REPORT

International application No.

PCT/US93/10762

## A. CLASSIFICATION OF SUBJECT MATTER

IPC(5) : A61K 9/70, 9/00, 31/40, 31/445, 31/135, 31/485

US CL : 424/449, 400; 514/413, 329, 648, 282

According to International Patent Classification (IPC) or to both national classification and IPC

## B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

U.S. : 424/449, 400; 514/413, 329, 648, 282

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

Please See Extra Sheet.

## C. DOCUMENTS CONSIDERED TO BE RELEVANT

| Category* | Citation of document, with indication, where appropriate, of the relevant passages  | Relevant to claim No. |
|-----------|---|-----------------------|
| Y         | US, A, 4,919,939 (BAKER) 24 APRIL 1990, see col. 15, line 55-col. 16, line 20.      | 1-25                  |
| Y         | US, A, 5,069,909 (SHARMA ET AL) 03 DECEMBER 1991, see particularly claim 1.         | 1-25                  |
| Y         | US, A, 5,091,182 (ONG ET AL) 25 FEBRUARY 1992, see col. 1, lines 30-45.             | 1-25                  |
| Y,P       | US, A, 5,203,768 (HAAK ET AL) 20 APRIL 1993, see col. 13, line 50-col. 14, line 53. | 1-25                  |
| Y         | US, A, 4,940,586 (CHENG ET AL) 10 JULY 1990, see particularly claim 5.              | 1-25                  |



Further documents are listed in the continuation of Box C.



See patent family annex.

|   |     |  |
|---|-----|--|
| * Special categories of cited documents:  | *T  | later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention  |
| *A* document defining the general state of the art which is not considered to be part of particular relevance   | *X* | document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone   |
| *E* earlier document published on or after the international filing date  | *Y* | document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art |
| *L* document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified) | *G* | document member of the same patent family  |
| *O* document referring to an oral disclosure, use, exhibition or other means  |     |  |
| *P* document published prior to the international filing date but later than the priority date claimed  |     |  |

Date of the actual completion of the international search

05 January 1994

Date of mailing of the international search report

FEB 14 1994

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# INTERNATIONAL SEARCH REPORT

International application No.  
PCT/US93/10762

## C (Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

| Category*   | Citation of document, with indication, where appropriate, of the relevant passages   | Relevant to claim No.                      |
|-------------|--|--|
| X<br>—<br>Y | G. K. McEVOY, "AHFS DRUG INFORMATION" published 1989 by the AMERICAN SOCIETY OF HOSPITAL PHARMACISTS, see pages 1025-1029, especially pages 1026 and 1027. | 1, 7, 8, 10-15,<br>17, 25<br>-----<br>1-25 |

## INTERNATIONAL SEARCH REPORT

International application No.  
PCT/US93/10762

### B. FIELDS SEARCHED

Electronic data bases consulted (Name of data base and where practicable terms used):

APS, STN(CAS, MEDLINE, BIOSIS)

search terms: transdermal, topical, patch, nasal, iontophoresis, ketorolac, morphine, fenantyl, methadone,  
buprenorphine analgesia, pain relief, analgesic